Remarks

Claims 70-79 have been cancelled. Claims 1-69 were cancelled in a previous response. New claims 80-95 have been added. Claims 80-95 are presented for the Examiner's review and consideration. Applicant believes the claim amendments and the accompanying remarks herein serve to clarify the present invention and are independent of patentability. No new matter has been added.

Amendments to the Specification

The title has been amended herein only to better coincide with the claims as currently pending.

No new matter has been added by the amendment to paragraph **[0037]** of the published application made herein. Paragraph **[0037]** was amended only to update the status of U.S. Patent Application Publication No. US 2001/0008888 as issued patent 6,455,518.

Amendments to the Claims

No new matter has been added by the addition of new claims 80-95. These new claims are fully supported in the specification as originally filed (published application, US 2004/0137066 A1) and in the cancelled claims.

The subject matter of new independent claim 80 is supported by cancelled claim 70 and in the published application. *See* paragraphs **[0045]**, **[0047]**, **[0050]**, **[0052]**, **[0084]**, **[0092]**-**[0094]**, **[0130]**, **[0133]**, **[0141]**, and Figure 8 of the published application.

The subject matter of new claims 81 and 82 is supported by cancelled claim 2 and paragraph **[0049]** of the published application.

The subject matter of new claim 83 is supported by cancelled claim 3 and paragraph **[0049]** of the published application.

The subject matter of new claim 84 is supported by cancelled claim 71 and paragraphs

[0049], **[0050]**, **[0082]**, **[0107]**, and **[0109]** of the published application. In paragraph **[0107]**, imatinib mesylate is referred to by brand name Gleevec®.

The subject matter of new claim 85 is supported by cancelled claim 70 and paragraphs **[0045]**, **[0046]**, **[0063]**, **[0083]-[0094]**, and Figure 7 of the published application.

The subject matter of new claims 86 and 87 is supported by paragraphs **[0068]**, **[0133]**, **[0139]-[0140]**, and Figure 12 of the published application.

The subject matter of new claims 88-95 is supported by cancelled claims 72-79.

Rejections under 35 U.S.C. §103(a)

Claims 70, 72, and 74-77 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Francis et al. (U.S. Patent No. 6,524,795; hereinafter "Francis") in view of Wolff et al. (international application WO 91/12779; hereinafter "Wolff"). Claims 70, 72, and 74-77 have been cancelled. New claims 80, 88, and 90-95 correspond to the cancelled claims. For reasons set forth below, Applicant respectfully submits that this rejection should be withdrawn.

It is noted that the references are described separately only to clarify what each reference teaches and not to argue the references separately.

Francis

In general, Francis discloses methods and kits for diagnosis and treatment of cardiovascular disorders. Specifically, the methods and kits are related to the diagnosis of disorders associated with IL-1 genotype patterns. *See* column 1, lines 14-17. Francis relies on the finding that there is an association of patterns of alleles at four polymeric loci in the IL-1 gene cluster with cardiovascular disorders. *See* column 8, lines 60-63 and column 27, lines 29-32. All of the methods and examples involve IL-1 genotyping and analysis for association with symptoms of cardiovascular disease. With regard to therapeutics for cardiovascular disorders, Francis mentions modulators of IL-1 and assays to identify such modulators. *See* column 43, section 4.4 and column 45, section 4.5. Francis does not disclose or suggest selection of

treatment agents based upon visual analysis of disease histopathology. Furthermore, Francis discloses nothing regarding treatment or prevention of cardiovascular disorders using stents, other than, in providing background for restenosis disorder therapeutics (column 24, line 45 to column 25, line 26), one very general mention of stent modification techniques. *See* column 25, lines 5-11.

Wolff

Wolff discloses a prosthesis for insertion into a lumen to limit restenosis of the lumen. The prosthesis carries restenosis-limiting drugs which elute after the device is positioned in the lumen. *See* abstract and Figure 1. Wolff teaches that the most widely accepted explanation for restenosis is that it is a natural healing process in response to the arterial injury that occurs during all types of angioplasty procedures. *See* page 5, lines 19-22. In order to treat this restenosis, Wolff notes that one must stop the proliferation of smooth muscle cells in the vessel walls. *See* page 7, lines 19-20. Wolff does not disclose evaluation of patients having restenosis or any other vascular condition. The preferred embodiment for the prosthesis described by Wolff is the stent **(10)** configuration consisting of a single filar, monofilament braided mesh design as shown in Figure 1. This stent consists of sixteen filaments **(12)**, eight of which are wound in one helical direction, and the remaining eight are wound in the opposite direction. *See* page 10, lines 22-27. A filament **(22)** can be formed with a metal core **(16)** and a coating **(14)** as shown in Figure 13. This coating can contain a drug and is required to overlie at least a portion of the metal core. *See* specification at page 3, lines 4-6. In Figure 13, the filaments are shown with partial or "cut off" coating at the ends to demonstrate that the metal core has a coating. *See* page 11, lines 35-38. Wolff does not disclose the use of sheaths or caps for completely enclosing the core of the filaments.

Claimed Invention

As currently claimed in independent claim 80, the invention provides, *inter alia*, a method of evaluating a vascular disease in a patient, and if determined necessary, treating or

preventing the vascular disease using a plurality of stent preforms interlaced to form a stent. The method includes steps of identifying a disease process in the pathology of the disease using visual analysis, evaluating the disease process identified to determine if treatment is necessary, if treatment is determined to be necessary, selecting a first agent to treat or prevent the disease and coating it on at least a portion of at least one of the plurality of stent preforms, selecting a second agent to treat or prevent the disease and coating it on at least a portion of at least one of the plurality of stent preforms, interlacing the coated preforms to form a stent, and implanting the stent in the patient to treat or prevent vascular disease. The selection of agents is based upon what is observed in the visual images. The visual imaging techniques used are not limited to what is claimed, any known visual imaging techniques can be used. Each of the stent preforms includes a metallic core, an outer sheath including the therapeutic agents (first and second agents), and caps disposed on both ends of the outer sheath to completely encapsulate the entire core. *See* paragraphs **[0045]**, **[0047]**, **[0050]**, **[0052]**, **[0084]**, **[0092]-[0094]**, **[0130]**, **[0133]**, **[0141]**, and Figure 8 of the published application.

The concept of restenosis or hyperproliferative vascular disease is now more clearly understood than it was a few years ago. It is no longer identified as simply a hyperproliferative disease, but more specifically as a fibroproliferative disease. The distinctive feature of restenosis is its histopathology, which can be visually observed directly in each individual patient. At first, as noted in Wolff, restenosis was thought simply to be a response of the vascular smooth muscle cells upon injury. There is now information available to demonstrate that restenosis is different in every individual depending on the underlying conditions (disease processes) that constitute the vascular disease. Thus, agents can be selected to treat or prevent the disease based upon a visual identification of the underlying disease process. These disease processes include acute myocardial infarction, thrombotic lesions, unstable angina, fibrotic disease, total occlusion of vascular lumens, hyperproliferative vascular disease, vulnerable plaque, diabetic vascular diffused disease, and/or combinations thereof. *See* paragraphs **[0045]-[0052]** and **[0084]** of the published application.

The stent used in the claimed method is formed by interlacing a plurality of stent

preforms that include the therapeutic agents (first and second agents) selected. Each preform comprises an elongated metallic core, including a contact surface and first and second ends, an outer sheath disposed about the contact surface of the metallic core, and caps disposed on the ends of the outer sheath. The sheath and caps completely surround the core to prevent the core from directly contacting the wall of a body lumen. *See* paragraphs **[0132]-[0134],** and Figure 8 of the published application.

Argument

The combination of the teachings of Francis and Wolff does not provide the method as currently claimed.

The Examiner asserts that Francis teaches both a method for examination of the vessel walls of a patient for restenosis and a method for treatment using a drug-covered stent.

Francis discloses a clinical study in which angiograms from patients were analyzed for restenosis and assigned disease categories (normal, mild disease, single vessel, two vessel, and three vessel disease) based on percent reduction in luminal diameter. This data was used to test the association of various risk factors and allelic variants among IL-1 gene clusters in each category of patients. *See* Example 5, The Mayo Clinic study at columns 58-60. First, although Francis discloses examination of coronary arteries, there is no evaluation for selection of therapeutic agents or treatment protocols based on this examination. Additionally, when providing a background definition of restenosis disorder therapeutics, Francis briefly states that the therapeutics can include drug-loaded polymer stents. *See* column 25, lines 5-11. However, there is no further mention of drug-loaded stents or any methods disclosed using drug-loaded stents.

The Examiner asserts that, according to Figures 1, 12, 15, and 17 of Wolff, the ends of the filaments must be encapsulated, otherwise the core would be shown as illustrated in an embodiment that does not encapsulate the ends (Figure 13). Thus, the Examiner concludes that the stent used in the claimed methods is illustrated by Wolff.

Applicant respectfully disagrees with the Examiner's interpretation of the disclosure of

Wolff. Wolff neither mentions nor illustrates a stent or a stent preform having capped or closed ends. Figure 12 of Wolff shows an enlarged fragment of filaments in a loose weave woven without any connection. *See* page 4, lines 24-25 and page 11, lines 35-36. Wolff discloses that a filament can be formed having a metal core and a coating. This coating can contain a drug and is required to overlie at least a portion of the metal core. *See* page 3, lines 2-6. The fragment illustrated in Figure 13 is that of Figure 12 further including the coating. In Figure 13, the filaments **(22)** are shown partially coated **(14)** with the ends of the metal core **(16)** exposed. *See* page 11, lines 36-38. Caps are neither illustrated nor even mentioned. Thus, Figure 13 is not showing an embodiment without a cap as asserted by the Examiner, but is simply clarifying the presence of the coating. Therefore, Wolff does not teach a stent or a stent preform having a metallic core completely encapsulated by an outer sheath having capped ends.

With regard to a method in which the stent is used, Wolff does not teach the steps of visually evaluating the current vascular state of a patient, identifying a disease process in the pathology of the disease and determining if treatment is necessary from the visual evaluation, and selecting therapeutic agents based upon what is visually observed. Furthermore, Wolff teaches that the most widely accepted explanation for restenosis is that it is a natural healing process in response to the arterial injury that occurs during all types of angioplasty procedures. Thus, Wolff suggests that the restenosis process is the same in every patient and does not contemplate design of a therapeutic stent based upon an individual patient's needs.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to use the stent of Wolff in the methods of treating a patient as disclosed by Francis. Applicant respectfully disagrees. As established above, the stent of Wolff is not equivalent to the stent used in the claimed method and Francis discloses a drug-loading stent only as one example of many treatments for restenosis. Thus, even if one of ordinary skill in the art combined the teachings of Wolff and Francis, the method, as currently claimed, would not be the result. Francis teaches diagnostic methods for disorders associated with IL-1 genotype patterns and teaches nothing more than the statement that restenosis can be treated using a drug-loaded stent. Neither reference teaches selection of a treatment protocol for an individual patient based

upon a visual examination of disease histopathology. Therefore, the stent of Wolff is only an example of a drug-loaded stent that can be used in a method to treat restenosis and is not the method of the invention or even the stent used in the invention. Furthermore, there is no motivation in either the cited references or other prior art to develop or practice the claimed method because there is no suggestion that a treatment method designed specifically for an individual patient, as in the claimed method, would work better than conventional treatments. The instant inventor was the first to design a stent based upon the needs of an individual patient.

Independent claim 80 recites, *inter alia*, a method of evaluating a vascular disease of a patient, and if determined necessary, treating or preventing a vascular disease of a patient with a plurality of stent preforms interlaced to form a stent, the method comprising: identifying a disease process in the pathology of the vascular disease using at least one visual imaging technique; evaluating the resulting images to determine if treatment is necessary, if determined to be necessary, selecting a first agent to treat or prevent the vascular disease based upon at least one visual image; coating at least a portion of at least one of the plurality of stent preforms with a therapeutically effective amount of the first agent; selecting a second agent to treat or prevent the vascular disease based upon at least one visual image; coating at least a portion of at least one of the plurality of stent preforms with a therapeutically effective amount of the second agent; interlacing the stent preforms to form a stent, wherein each of the plurality of stent preforms comprises: an elongated metallic core including a contact surface and first and second ends, an outer sheath disposed about the contact surface, the outer sheet including the first and second agents, and caps disposed on a first end and a second end of the outer sheath, thereby encapsulating the entire core; and implanting the stent in the patient to treat or prevent the vascular disease.

Accordingly, Applicant respectfully submits that claim 80 is patentable over Francis in view of Wolff. As claims 88 and 90-95 depend from claim 80, these dependent claims necessarily include all of the elements of the base claim. Accordingly, Applicant respectfully submits that the dependent claims are patentable over the cited references at least for the same reasons.

In light of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 70, 72, and 74-77 (new claims 80, 88, and 90-95) under 35 U.S.C. §103(a).

Claim 71 (new claim 84) was rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Francis in view of Wolff as applied above and further in view of Kahan et al. (Transplantation Proceedings 23(1, part 2):1090-1091 1999; hereinafter "Kahan"). Claim 73 (new claim 89) was rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Francis in view of Wolff as applied above and further in view of Liprie et al. (U.S. Patent No. 6,491,662; hereinafter "Liprie"). Claims 78 and 79 (new claims 94 and 95) were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Francis in view of Wolff as applied above and further in view of Barclay et al. (U.S. Patent Application Publication No. 2002/77693; hereinafter "Barclay").

As discussed above, claim 80 (cancelled claim 70) is submitted to be patentable over Francis in view of Wolff. The inclusion of the teachings of Kahan, Liprie, and/or Barclay fails to overcome the deficiencies of either Francis or Wolff. Claims 84, 89, 94, and 95 depend from claim 80, and include all of the elements of their base claim. Accordingly, Applicant submits that these dependent claims are patentable at least for the same reasons.

In light of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejections of claims 71, 73, 78, and 79 (new claims 84, 89, 94, and 95) under 35 U.S.C. §103(a).

Conclusion

In light of the foregoing amendments and remarks, this application is now in condition for allowance and early passage of this case to issue is respectfully requested. If any questions remain regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

The fee for a request for continued examination pursuant to Section 1.17(e) in the amount of $405, the fee for a one month extension of time pursuant to Section 1.17(a)(1) in the amount of $65, and the fee for six extra claims pursuant to Section 1.16(i) in the amount of $156 are believed to be due and are being paid via credit card. No other fees are believed to be due at this time. However, please charge any other required fee (or credit overpayments) to the Deposit Account of the undersigned, Account No. 503410 (Docket No. 795-A03-004).

Respectfully submitted,

/Katharine F. Davis Wong/

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